ACUTE TOXICITY SUMMARY

OZONE

(triatomic oxygen)

CAS Registry Number: 10028-15-6

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**180 μg/m³**
Critical effect(s)	eye irritation and minor changes in lung function tests
Hazard Index target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless to light blue gas
Molecular formula	O_3
Molecular weight	48.0
Density	2.144 g/L @ 0°C (gas)
Boiling point	-111.9°C
Melting point	-192.7°C
Vapor pressure	>760 mm Hg @ 25°C (NIOSH, 1994)
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	insoluble in water; soluble in alkaline solvents, oils
Odor threshold	0.0076-0.036 ppm (15-71 μg/m³) (AIHA, 1989)
Odor description	pungent
Metabolites	unknown
Conversion factor	1 ppm = 1.96 mg/m³ @ 25°C

III. Major Uses or Sources

Ozone is a natural (non-anthropogenic) constituent of the atmosphere with a level between 0.01 and 0.04 ppm. Ozone (O_3) is produced in photochemical reactions of hydrocarbons and nitrogen oxides in the engines of motor vehicles (CARB, 1987) and by certain welding operations. Ozone is used commercially as a disinfectant for air and water. It is also used for bleaching textiles, oils, waxes, and in organic synthesis (ACGIH, 1991).

IV. Acute Toxicity to Humans

Impairment of lung function and subsequent impairment of exercise performance were measured in exercising adult athletes (age 19-30) exposed to 0.2 ppm (0.4 mg/m³) ozone for 1 hour (Gong *et al*., 1986). A decrement in post-exercise forced expiratory volume in 1 second (FEV_1) of

21.6% was observed; a 5.6% decrease in FEV_1 was observed in athletes following a 1-hour exposure to 0.12 ppm (0.24 mg/m³) ozone with exercise. Significant reductions in peak minute ventilation, oxygen uptake, and tidal volume were observed in athletes exposed to 0.2 ppm ozone, but not in those exposed to 0.12 ppm.

Healthy young males (age 19-30) exposed to ozone at concentrations as low as 0.12 ppm (0.24 mg/m³) for 2.5 hours exhibited statistically significant changes in forced vital capacity (FVC), FEV_1, forced expiratory flow rates at 75% to 25% of lung volume (FEF_{25-75}), and increased coughing (McDonnell *et al*., 1983). Statistically significant increases in specific airway resistance (SRaw) and reporting of shortness of breath and pain upon deep inspiration were observed in subjects exposed to ozone at concentrations of 0.24 ppm (0.47 mg/m³) or greater. A more recent study (McDonnell *et al*., 1991) reported decrements in FVC, FEV_1, and significant increases in SRaw and respiratory symptoms in 38 healthy young men following a 6.6-hour exposure to 0.08 ppm (0.2 mg/m³) ozone involving 5 hours of exercise.

A statistically significant 3% decrease in FEV_1 was observed in male children (age 8-11) following a 2.5 hour exposure to 0.12 ppm (0.24 mg/m³) ozone with intermittent exercise (McDonnell *et al*., 1985). No significant increase in cough was noted as a result of ozone exposure.

A review by Lippmann (1993) reported that the ozone-associated lower airway response in the normal population engaged in outdoor recreational activity is greatly underestimated by 1 to 2-hour controlled chamber exposure studies, which indicate very little or no functional decrement at 0.120 ppm (249 µg/m³) ozone. One study cited by Lippmann (1993) reported significant ozone-associated decrements in FVC, FEV_1, peak expiratory flow rate (PEFR), FEF_{25-75}, and FEV_1/FVC in healthy adults following outdoor exercise in ambient ozone concentrations of 0.021-0.124 ppm (41-243 mg/m³) for an average of 29 minutes (Spektor *et al*., 1988). In subjects with low ventilation rates (<60 L/minute), the effects observed were about two times greater than those reported in chamber studies using comparable ventilation rates. Recent studies have confirmed that asthmatics react more severely than normal subjects to ozone (Scannell *et al*., 1996) and that there is a wide variability in spirometric responsiveness (as measured by changes in FVC, FEV_1, and FEF_{25-75}) among individuals to ozone (Weinmann *et al*., 1995).

Predisposing Conditions for Ozone Toxicity

Medical: Persons with preexisting respiratory conditions, such as asthma or chronic obstructive lung disease, may be more sensitive to the adverse effects of ozone exposure (CARB, 1987a). Persons doing vigorous exercise or manual labor outdoors are likely to have increased ventilation rates and to be exposed to a higher dose of ozone and thus may be at increased risk for ozone toxicity.

Chemical: Co-exposure to some aeroallergens and respiratory irritants, such as sulfur dioxide, may exacerbate the adverse respiratory effects of ozone in asthmatics (CARB, 1987a).

V. Acute Toxicity to Laboratory Animals

The 3-hour LC_{50} values for rats, mice, guinea pigs, and rabbits are reported as 21.8 ppm, 21 ppm, 51.7 ppm, and 36 ppm (42.7, 41, 101, and 71 mg/m^3) ozone, respectively (Mittler *et al*., 1956).

A 21% increase in mortality over controls was observed in mice challenged with aerosolized streptococci concurrent with a 3-hour exposure to 0.1 ppm (0.2 mg/m^3) ozone (Miller *et al*., 1978). Mice challenged with streptococci immediately following the 3-hour ozone exposure, however, did not exhibit a significant increase in mortality.

Due to the abundance of human exposure studies, additional animal studies were not summarized here.

VI. Reproductive or Developmental Toxicity

No reports of human reproductive or developmental toxicity due to ozone were located in the literature (Shepard, 1994). Increased resorption rates were observed following exposure of pregnant rats to 1.97 ppm (3.86 mg/m^3) ozone 8 hours per day on days 6-9, 9-12, or 6-15 of gestation (Kavlock *et al*., 1979). A later study from the same laboratory reported that pregnant rats exposed to 1.0 or 1.5 ppm (2 or 2.9 mg/m^3) ozone on days 17-20 of gestation had offspring which exhibited retardation of reflex development and slowing in open field behavior (Kavlock *et al*., 1980).

Veninga (1967) reported blepharophimosis (inability to open the eye to the normal extent) and jaw anomalies in mouse fetuses following maternal exposure to 0.2 ppm (0.4 mg/m^3) ozone 7 hours per day, 5 days per week. Because the original reference was not available for review, key experimental details (including the days of gestation during which exposure occurred) are not known.

Comparisons of pregnant, lactating, and virgin female rats exposed to 1 ppm (2 mg/m^3) ozone for 6 hours demonstrated enhanced sensitivity to ozone-induced pulmonary inflammation in pregnant and lactating rats (Gunnison *et al*., 1992). Pulmonary lavage fluid indicators of inflammation measured include total protein, LDH, total leukocytes, total PMN, and β-glucuronidase activity.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.09 ppm (180 μg/m³)
(California Ambient Air Quality Standard)

Study	Gong *et al*., 1986; McDonnell *et al*., 1983; McDonnell *et al*., 1985; California Air Resources Board (CARB), 1987a, 1987b.
Study population	normal adults
Exposure method	inhalation in controlled exposure chambers
Critical effects	decrease in pulmonary function including a 10% decrease in FEV_1
LOAEL	0.12 ppm (0.24 mg/m³) ozone
NOAEL	not observed
Exposure duration	1 hour
Extrapolated 1 hour concentration	0.12 ppm
LOAEL uncertainty factor	1.3 (margin of safety)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1.3 (see below)
Reference Exposure Level	0.09 ppm (0.18 mg/m³; 180 μg/m³)

The methodology for developing California Ambient Air Quality Standards differs from that used to develop other acute RELs. The existing CAAQS is based largely upon controlled chamber studies. Inhalation of 0.12 ppm (0.24 mg/m³) ozone by normal human subjects in exposure chambers resulted in a decrease in pulmonary function including a 10% decrease in FEV_1. A margin of safety was added yielding the 1-hour standard of 0.09 ppm (0.18 mg/m³). The CAAQS was also designed to protect against eye irritation, a symptom frequently reported when the 1-hour ozone average is 0.1 ppm or greater (although the eye irritation reported may be a result of non-ozone compounds). A recent study (Spektor *et al*., 1988) reported significant ozone-associated decrements in FVC, FEV_1, PEFR, FEF_{25-75}, and FEV_1/FVC in healthy adults following outdoor exercise in ambient ozone concentrations of 21-124 ppb (41-243 μg/m³) for an average of 29 minutes. In subjects with low ventilation rates (<60 L/minute), the effects observed were about two times greater than those reported in chamber studies using comparable ventilation rates. This new information will be considered when the CAAQS is reevaluated by OEHHA.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

U.S.EPA (1975) has identified a significant harm level of 0.6 ppm (1.2 mg/m³). U.S.EPA states that "at this exposure-time combination [0.6 ppm (1.2 mg/m³) ozone for a 1-hour exposure], it is judged that acutely incapacitating symptoms will be experienced by significant portions of the population, especially those engaged in light to moderate exercise, and that the health status of

particularly vulnerable cardiopulmonary subjects may be seriously compromised." The key study, on which this level is based, is a study of 10 subjects who reported substernal soreness (6/10), cough (8/10), and marked shortness of breath during a 2-hour exposure to 0.75 ppm (1.5 mg/m^3) ozone involving alternating 15-minute periods of exercise and rest (Bates *et al*., 1972). The authors concluded that an ozone concentration of 0.75 ppm (1.5 mg/m^3) produced serious adverse effects under conditions of mild exercise. The choice of the significant harm level is unacceptable as a level protective against severe health effects for exposure of the general public due to the lack of the presentation of a formal protocol for its derivation by U.S.EPA (1975).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

The NIOSH-IDLH for ozone (NIOSH, 1995) is 10 mg/m^3 (5 ppm) based on acute inhalation toxicity data in humans (Deichmann and Gerarde, 1969; Kleinfeld *et al*., 1957). According to NIOSH, "Pulmonary edema developed in welders who had a severe acute exposure to an estimated 9 ppm ozone plus other air pollutants (Kleinfeld *et al*., 1957). It has been reported that on the basis of animal data, exposure at 50 ppm for 60 minutes will probably be fatal to humans (King, 1963)." The derivation of this value is not clearly explained.

VIII. References

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 1155-1157.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 26.

Bates DV, Bell DM, Burnham CD, Hazucha M, Mantha J, Pengelly LD, Silverman F. Short-term effects of ozone on the lung. J Appl Physiol 1972;32:176-181. [cited in U.S.EPA, 1975.]

(CARB) California Air Resources Board. Ambient Air Quality Standard for ozone: Health and welfare effects. Staff Report. Sacramento: CARB; September 1987a.

(CARB) California Air Resources Board. Effects of ozone on health. Technical Support Document. Sacramento: CARB; September 1987b.

Deichmann WB, Gerarde HW. Ozone. In: Toxicity of drugs and chemicals. New York (NY): Academic Press, Inc.; 1969. p. 446-448.

Folinsbee LJ, Silverman F, Shepard RJ. Exercise responses following ozone exposure. J Appl Physiol 1987;38(6):996-1001.

Gong H, Bradley PW, Simmons MS, Tashkin DP. Impaired exercise performance and pulmonary function in elite cyclists during low-level ozone exposure in a hot environment. Am Rev Respir Dis 1986;134:726-733.

Gunnison AF, Weideman PA, Sobo M. Enhanced inflammatory response to acute ozone exposure in rats during pregnancy and lactation. Fundam Appl Toxicol 1992;19:607-612.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 7/31/94).

Higgins ITT, D'Arcy JB, Gibbons DI, Avol EL, Gross KB. Effects of exposures to ambient ozone on ventilatory lung function in children. Am Rev Respir Dis 1990;141:1136-1146.

Kavlock R, Daston G, Grabowski CT. Studies on the developmental toxicity of ozone. I. Prenatal effects. Toxicol Appl Pharmacol 1979;48:19-28.

Kavlock RJ, Meyer E, Grabowski CT. Studies on the developmental toxicity of ozone: postnatal effects. Toxicol Lett 1980;5:3-9.

King ME. Toxicity of ozone. V. Factors affecting acute toxicity. Ind Med Surg 1963;32:93-94.

Kleinfeld M, Giel C, Tabershaw IR. Health hazards associated with inert-gas-shielded metal arc welding. AMA Arch Ind Health 1957;15(1):27-31.

Lippmann M. Health effects of trophospheric ozone: Review of recent research findings and their implications to ambient air quality standards. J Expo Anal Environ Epidemiol 1993;3(1):103-129.

McDonnell WF, Horstman DH, Hazucha MJ, Seal E, Haak ED, Salaam SA, *et al*. Pulmonary effects of ozone exposure during exercise: dose-response characteristics. J Appl Physiol 1983;54:1345-1352.

McDonnell WF, Chapman RS, Leigh MW, Strope GL, Collier AM. Respiratory responses of vigorously exercising children to 0.12 ppm ozone exposure. Am Rev Respir Dis 1985;132(4):875-879.

McDonnell WF, Kehrl HW, Abdul-Salaam S, Ives PJ, Folinsbee LJ, Devlin RB, *et al*. Respiratory response of humans exposed to low levels of ozone for 6.6 hours. Arch Environ Health 1991;46(3):145-150.

McDonnell WF, Muller KE, Bromberg PA, Shy CM. Predictors of individual differences in acute response to ozone exposure. Am Rev Respir Dis 1993;147:818-825.

Miller FJ, Illing JW, Gardner DE. Effect of urban ozone levels on laboratory-induced respiratory infections. Toxicol Lett 1978;2:163-169.

Mittler S, Hedrick D, King M, Gaynor A. Toxicity of ozone. I Acute toxicity. Ind Med Surg 1956;25:301-306.

(NIOSH) National Institute of Occupational Safety and Health. Chemical listing and documentation of revised IDLH values (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

(NIOSH) National Institute of Occupational Safety and Health Pocket Guide (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 7/31/94).

(NRC) National Research Council. Emergency and continuous exposure limits for selected airborne contaminants. Ozone. Washington, DC: National Academy Press; 1984. p. 99-106.

Scannell C, Chen L, Aris RM, Tager I, Christian D, Ferrando R, *et al*. Greater ozone-induced inflammatory responses in subjects with asthma. Am J Respir Crit Care Med 1996;154(1)24-29.

Shepard's catalog of teratogenic agents (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 7/31/94).

Spektor DM, Lippmann M, Thurston GD, Lioy PJ, Stecko J, O'Connor G, *et al*. Effects of ambient ozone on respiratory function in healthy adults exercising outdoors. Am Rev Respir Dis 1988;138:821-828.

(U.S.EPA) US Environmental Protection Agency. Prevention of air pollution emergency episodes. Part 51 Chapter I, Title 40 of the Code of Federal Regulations. Federal Register 1975;40(162):36333-36335.

Veninga, TS. Toxicity of ozone in comparison with ionizing radiation. Strahlentherapie 1967;134:469-477. [cited in Shepard's catalog of teratogenic agents, 1994.]

Weinmann GG, Bowes SM, Gerbase MW, Kimball AW, Frank R. Response to acute ozone exposure in healthy men. Results of a screening procedure. Am J Respir Crit Care Med 1995;151(1):33-40.